

WEST Search History

DATE: Monday, February 05, 2007

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|--------------------------|---------------------------|---|----------------------------|
| | | <i>DB=USPT; PLUR=YES; OP=ADJ</i> | |
| <input type="checkbox"/> | L1 | (544/242.ccls. or 546/273\$3.ccls. or 546/269\$3.ccls. or 546/30\$3.ccls.) and (benzimidaz\$7 same (bacteri\$5 or antibacte\$5)) | 11 |

END OF SEARCH HISTORY

INTERNATIONAL SEARCH REPORT

PCT/US2004/002541

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/14 C07D401/14 C07D405/14 C07D403/10 C07D491/04
C07D413/14 C07D417/14 C07D471/04 C07D487/04 A61K31/4184
A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 02/060879 A (BADIA MICHAEL ; STAMOS DEAN (US); VERTEX PHARMA (US); CHARIFSON PAUL ()) 8 August 2002 (2002-08-08) cited in the application page 6 - page 7; examples | 1-31 |
| P, X | WO 03/105846 A (DEININGER DAVID D ; OLIVER-SHAFFER PATRICIA (US); STAMOS DEAN (US); VE) 24 December 2003 (2003-12-24) examples ----- -/-- | 1-31 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

7 December 2004

Date of mailing of the international search report

21/12/2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

PCT/US2004/002541

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | KUS C ET AL: "SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF 5-FLUORO-1,2,6-TRISUBSTITUTED BENZIMIDAZOLE CARBOXAMIDE AND ACETAMIDE DERIVATIVES" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 334, no. 11, 2001, pages 361-365, XP001113052 ISSN: 0365-6233 page 361; example 12c; table 1 ----- | 1-31 |
| A | SUN Q ET AL: "SYNTHESIS AND EVALUATION OF TERBENZIMIDAZOLES AS TOPOISOMERASE I INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 38, no. 18, September 1995 (1995-09), pages 3638-3644, XP002010635 ISSN: 0022-2623 the whole document ----- | 1-31 |
| A | HUBSCHWERLEN ET AL.: "Pyrimido'1,6-albenzimidazoles: A New Class of DNA Gyrase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 8, 1992, pages 1385-1392, XP002309406 table II ----- | 1-31 |

INTERNATIONAL SEARCH REPORT

PCT/US2004/002541

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US2004/002541

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---------------------|----------------------------|---------------|---------------------|
| WO 02060879 | A | 08-08-2002 | BR | 0116216 A | 17-08-2004 |
| | | | CA | 2433197 A1 | 08-08-2002 |
| | | | CN | 1481368 T | 10-03-2004 |
| | | | EP | 1341769 A2 | 10-09-2003 |
| | | | HU | 0303494 A2 | 28-01-2004 |
| | | | JP | 2004518684 T | 24-06-2004 |
| | | | MX | PA03005298 A | 06-10-2003 |
| | | | NO | 20032668 A | 12-06-2003 |
| | | | WO | 02060879 A2 | 08-08-2002 |
| | | | US | 2003119868 A1 | 26-06-2003 |
| | | | US | 2004043989 A1 | 04-03-2004 |
| | | | ZA | 200303933 A | 21-05-2004 |
| | | | | | |
| WO 03105846 | A | 24-12-2003 | WO | 03105846 A1 | 24-12-2003 |

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/002541

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-31 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-31 |
| Industrial applicability (IA) | Yes: Claims | 1-22 |
| | No: Claims | |

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

see separate sheet

1) Reference is made to the following documents:

D1: WO 02/060879 A

D2: WO 03/105846 A

D3: KUS C ET AL: "SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF 5-FLUORO-1,2,6-TRISUBSTITUTED BENZIMIDAZOLE CARBOXAMIDE AND ACETAMIDE DERIVATIVES" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 334, no. 11, 2001, pages 361-365, XP001113052 ISSN: 0365-6233

D4: SUN Q ET AL: "SYNTHESIS AND EVALUATION OF TERBENZIMIDAZOLES AS TOPOISOMERASE I INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 38, no. 18, September 1995 (1995-09), pages 3638-3644, XP002010635 ISSN: 0022-2623

D5: HUBSCHWERLEN ET AL.: "Pyrimido[1,6-a]benzimidazoles: A New Class of DNA Gyrase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 8, 1992, pages 1385-1392, XP002309406

1.1) Reference to section VI

In view of its publication date of 24/12/2003, the content of D2 will not be used in the present Written Opinion.

2) Reference to section III

Claims 23-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3) Novelty (Reference to section V)

Present compounds of formula I can be considered as a selection over compounds disclosed in D1 (cf. for instance pages 6 and 7 of D1). However, no compound has been observed in the examples of D1 (cf. table 1 on page 17) falling within the meaning of present formula I.

D3 describes 5-fluoro-1,2,6-trisubstituted benzimidazole carboxamide and acetamide derivatives, but none of them possesses a heteroaryl ring at the position of present A substituent.

D4 and D5 disclose benzimidazole derivatives, which differ from current compounds of formula I in the substituent pattern on said heterocyclic ring.

Accordingly, the subject-matter of present claims 1-31 meets the requirements of Article 33(2) PCT.

4) Inventive step (Reference to section V)

D1, which may be considered to represent the closest state of the art, describes general compounds of formula I, being structurally close to present ones and being at the same time inhibitors of bacterial gyrase activity. They are in fact used in the treatment of bacterial infections or nosocomial infections in hospitals, where the formation and transmission of resistant bacteria are becoming increasingly prevalent (cf. pages 1-6 of D1).

The problem to be solved by the present application may be regarded as the provision of compounds showing an improved activity in the inhibition of bacterial gyrases.

As stated in paragraph 3 above, the subject-matter of present claim 1 consists in the selection of a particular substituent (such as a heteroaryl ring at the position of present A substituent) from the range of those described for the group R^3 in D1. Such a selection can only be regarded as inventive, if the current compounds present unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application.

The Applicant has also underlined on page 12, last lines of the description, that "compounds of the present invention fall within the genus of compounds described in PCT/US 01/48855 (D1). However Applicants have discovered that the presence of the ring A moiety imparts surprising and unexpectedly increased gyrase inhibitory, TopoIV activity, and antimicrobial potency".

No Data or further evidence of said unexpected properties are nevertheless given in the description.

The Applicant's attention is also drawn to document D3, disclosing benzimidazole derivatives useful as antimicrobial and antifungal agents: in particular, on page 361 of D3, last paragraph, it is mentioned that compound 12c exhibits the best antifungal activity. When having a look at compound 12c on page 363 in combination with table 1, it is noticed that it is structurally very close to current formula I (cf. the $-NH-C(=O)OCH_3$ chain between the two nitrogen atoms of the benzimidazole ring, and the piperidine group on the phenyl ring).

Accordingly, the skilled person would have been encouraged from D3 in developing further compounds structurally similar to compound 12c of D3 and would have reasonably

expected that they demonstrated the same activity.

Thus, the subject-matter of present claims 1-31 does not meet the requirements of Article 33(3) PCT.

5) Industrial applicability (Reference to section V)

For the assessment of the present claims 23-31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Synthesis and antimicrobial activities of 5-fluoro-1,2,6-trisubstituted benzimidazole carboxamide and acetamide derivatives

Some 5-fluoro-6-substitute-1*H*-benzimidazole-2-carbamates (**12a–e**), 5-fluoro-6-substituted 1*H*-benzimidazole-2-acetate (**13a–e**) and 2-acetamide (**14a–f**) derivatives, 2-acetamido-5-fluoro-6-(morpholin-4-yl)-1-propyl-1*H*-benzimidazole (**15**), and 1-cyclopropyl-2-ethyl-5-fluoro-6-(4-methylpiperazin-1-yl)-1*H*-benzimidazole (**16**) were synthesized, and their antimicrobial and antifungal activities evaluated. Compound **12c** exhibited the best activity against *Candida albicans*.

Key Words: Benzimidazole carbamates; Benzimidazole acetates; Benzimidazole acetamides; 1*H*-benzimidazole derivatives; Antifungal and antibacterial activity

Received: May 21, 2001 [FP585]

Introduction

The benzimidazole carbamates, an important group of anthelmintic agents, act by blocking polymerization of microtubules in susceptible organisms and these compounds were found to inhibit *Pneumocystis carinii* in vitro and in vivo culture systems^[1,2]. Anthelmintic benzimidazoles were also examined against *Giardia lamblia*^[3], *Cryptococcus neoformans*^[4], and *Trichomonas vaginalis*^[5] and they are approved as useful for the treatment of these infections. Albendazole was found to be useful for treating systemic infections and it was established that albendazole is highly effective a therapeutic agent in the treatment of cysticercosis^[6] and echinococcosis^[7].

Many derivatives of benzimidazole are well known as antimicrobial^[8,9] and antifungal^[10] agents and show a wide variety of biological activity as well as anthelmintic potency. The synthesis of the compounds having both fluorine and piperazine substituents at 5- and 6-positions have been reported^[11] because of the influence on antibacterial activity of these groups for the second generation fluoroquinolones. In order to obtain more potent compounds, these observations prompted us to synthesis some new benzimidazole carbamate, benzimidazole acetate and acetamide derivatives having 5-fluoro and 6-substitute piperazine, piperidine or morpholine and evaluate their antimicrobial and antifungal activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*.

Results and discussion

Synthesis of the compounds **9a**^[12], **9b**^[13] has previously been reported, and the compound **9c** was prepared in a

similar manner. Substitution of **9a–c** with appropriate piperazine, piperidine derivatives, or morpholine gave *o*-nitroanilines (**10a–g**), and their reduction afforded *o*-phenylenediamine derivatives (**11a–g**). Because of the instability of **11a–g**, these compounds were used for the next step without purification, except **11c**^[11] (Scheme 1).

The benzimidazole carbamate derivatives (**12a–e**) were prepared by direct condensation of the corresponding 4,5-disubstituted-*o*-phenylenediamines (**11c–e**) with 1,3-dicarbalkoxy-*S*-methyl-isothiourea^[14–16]. The reaction of **11a–c**, **11f–g** with ethyl β -amino- β -ethoxyacrylate hydrochloride^[17] gave the desired ester derivatives of benzimidazoles **13a–e**. Amidification of these esters with several *N,N*-dialkylaminoethyl or propylamine derivatives gave the acetamidobenzimidazoles **14a–f**. The reaction of ester **13e** with ammonia gave **15** (Scheme 1).

Catalytic hydrogenation of **13a**, in the presence of palladium on charcoal (Pd/C) in DMF gave **16** (Scheme 1). Conformational analysis of **16** was performed with its X-ray crystallography data^[18]. Structures and formulas, purification procedures, physical, and spectral data of the targeted compounds are shown in Table 1 and Table 2, respectively.

Compounds **12a–e**, **13b–e**, **14a–f**, **15**, and **16** were evaluated for their in vitro antimicrobial and antifungal activity against *B. subtilis*, *S. aureus*, *E. coli*, and *C. albicans* by the agar diffusion method which was already reported by us^[19] using a 2000 μ g/ml solution in propylene glycol (Table 1). All the compounds showed the growth inhibition zone against *C. albicans*. Among them, methyl 5-fluoro-6-(4-methylpiperidin-1-yl)-1*H*-benzimidazole-2-carbamate (**12c**) exhibited the best antifungal activity with 15 mm inhibition zone diameter, which was less than those of fluconazole and ketoconazole. In addition compounds **13b–e**, **14a–f** also exhibited moderate activity against *B. subtilis*. Anthelmintic activities of the synthesized compounds are being investigated and the results will be published later.

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Table 1. Structure, antibacterial and antifungal activity^a of **12a–e**, **13b–e**, **14a–f**, **15**, and **16**.

| Comp | R | R ₁ | R ₂ | n | ^b B.s. | ^c S.a. | ^d E.c. | ^e C.a. |
|------------|-------------|--------------------|----------------|---|----------------------|----------------------|----------------------|----------------------|
| 12a | | N-Methylpiperazine | Methyl | | * | * | * | 11 |
| 12b | | N-Methylpiperazine | Ethyl | | * | * | * | 11 |
| 12c | | 4-Methylpiperidine | Methyl | | * | * | * | 15 |
| 12d | | 4-Methylpiperidine | Ethyl | | * | * | * | 13 |
| 12e | | N-Phenylpiperazine | Ethyl | | * | * | * | 9 |
| 13b | Cyclopropyl | 3-Methylpiperidine | | | 12 | 9 | 10 | 12 |
| 13c | H | N-Methylpiperazine | | | 9 | * | * | 11 |
| 13d | H | 3-Methylpiperidine | | | 11 | * | 8 | 11 |
| 13e | n-propyl | Morpholine | | | 11 | * | 9 | 11 |
| 14a | H | N-Methylpiperazine | Ethyl | 2 | 9 | 9 | * | 12 |
| 14b | Cyclopropyl | N-Methylpiperazine | Methyl | 2 | 10 | * | * | 10 |
| 14c | Cyclopropyl | 3-Methylpiperidine | Methyl | 2 | 8 | 9 | * | 13 |
| 14d | Cyclopropyl | 3-Methylpiperidine | Ethyl | 2 | 11 | * | * | 10 |
| 14e | Cyclopropyl | N-Methylpiperazine | Ethyl | 2 | 10 | * | * | 10 |
| 14f | Cyclopropyl | N-Methylpiperazine | Methyl | 3 | 7 | * | * | 11 |
| 15 | | | | | NT | NT | NT | 12 |
| 16 | | | | | NT | NT | NT | 11 |
| F | | | | | * | * | * | 18 |
| K | | | | | * | * | * | 24 |
| A | | | | | 13 | 15 | 11 | * |

^a Growth-inhibition zone diameter (mm); ^b *Bacillus subtilis*; ^c *Staphylococcus aureus*; ^d *Escherichia coli*; ^e *Candida albicans*; *No activity; NT: not tested; F: fluconazole; K: ketoconazole; A: ampicilline.

Experimental

Silica gel plates (Merck F254) and silica gel 60 (Merck; 230–400 mesh ATSM) were used for analytical and column chromatography, respectively. Melting points (uncorrected) were determined with a Büchi SMP-20 melting point apparatus. Microanalyses were performed on a Leco CHNS 932 analyzer and satisfactory results within ±0.4% of calculated values (C,H,N) were obtained. All the instrumental analyses were performed by Tubitak (Instrumental Analysis Lab., Ankara) with a Bruker AC400NMR spectrophotometer and VG Platform II mass spectrometer. The HCl salts of the acetamide derivatives were prepared by using ethanolic HCl. 2,5-difluoroacetanilide (**2**)^[20], 2,5-difluoro-4-nitroacetanilide (**3**)^[21], 2,5-difluoro-4-nitroaniline (**4**)^[21], 2,5-difluoro-4-chloronitrobenzene (**5**)^[21], *N*-(3-chloro-4-fluorophenyl)acetamide (**7**)^[12], and *N*-(5-chloro-4-fluoro-2-nitrophenyl)acetamide (**8**)^[12] were synthesized according to the methods given in the literature.

5-Chloro-4-fluoro-2-nitro-*N*-propylaniline **9c**

A solution of **5** (0.5 g, 2.58 mmol) in a mixture of triethylamine (5 ml) and *n*-propylamine (0.23 g, 3.9 mmol) was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc and extracted with water. The organic layer was dried over anhydrous Na₂SO₄ and evaporated. The residue was crystallized from EtOH, affording 0.5 g (83%) of **9c**. Mp 86–88 °C. NMR (CDCl₃) δ 1.08 (t, 3H), 1.8 (m, 2H), 3.25 (q, 2H), 6.9 (d, 1H, *J*_m = 6 Hz), 7.9 (br.s, 1H), 8.0 (d, 1H, *J*_o = 9 Hz), 8.2 (br.s, 1H). Anal. (C₉H₁₀ClFN₂O₂) C, H, N.

Synthesis of **10a–g**

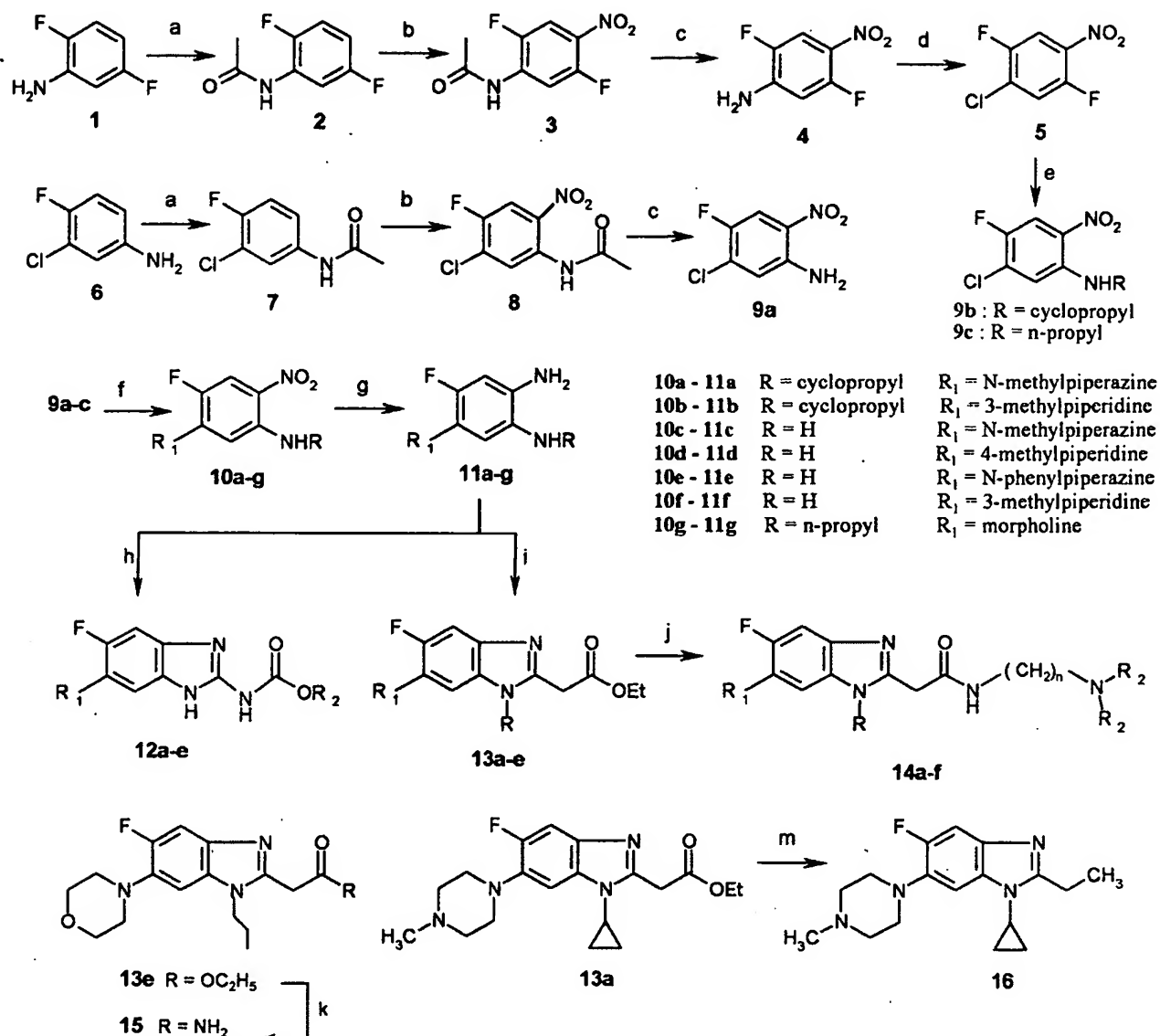
A solution of **9a–c** (2.5 mmol) in a mixture of triethylamine (0.5 ml) and appropriate piperazine, piperidine derivatives, or morpholine (5 mmol) was stirred at 60 °C overnight. The resulting suspension was partitioned between water and EtOAc (1:2). The organic layer was subsequently washed with water, then dried over anhydrous Na₂SO₄ and evaporated (Table 2).

Synthesis of substituted *o*-phenylenediamines **11a–g**

A solution of **10a–g** (1.98 mmol) in concentrated hydrochloric acid (10 ml) was treated portionwise with SnCl₂ (11.85 mmol) and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and neutralized with 10% NaOH solution, extracted with EtOAc, washed with water, dried over anhydrous Na₂SO₄, and evaporated and used for the next step without further purification because of their instability, except **11c**^[11] (Table 2).

Synthesis of 1*H*-benzimidazole-2-carbamate derivatives **12a–e**

Appropriate 1,3-dicarbalkoxy-*S*-methylisothiourea (2 mmol) was added to a solution of **11c–e** (1 mmol) in ethanol (15 ml) and refluxed for 8 h under a nitrogen atmosphere. The reaction mixture was cooled and the separated solid was filtered off (Table 2).



Scheme 1. Synthesis of the target compounds. a: Acetic anhydride/pyridine, b: conc.H₂SO₄/conc.HNO₃, c: H₂SO₄/H₂O, d: NaNO₂/HCl, CuCl, e: cyclopropylamine, *n*-propylamine/triethylamine, f: appropriate piperazines, piperidines or morpholine, g: SnCl₂/HCl or H₂.Pd/C, DMF, h: 1,3-dicarbalkoxy-*S*-methylisothiourea/EtOH, i: ethyl β-amino-β-ethoxyacrylate hydrochloride/DMF, j: appropriate ethylenediamines, k: NH₄OH m: H₂.Pd/C, DMF.

Synthesis of ethyl 1H-benzimidazole-2-acetate derivatives 13a-e

A solution of 10a-c, 10f-g (1 mmol) in 0.5 ml DMF was hydrogenated over 10% Pd/C at 50 °C for 4 h. At the end of the reduction, the catalyst was filtered through a bed of Celite and the filtrate was evaporated. The unstable residue was dissolved in DMF (0.5 ml) and reacted with ethyl β-amino-β-ethoxyacrylate hydrochloride (2 mmol). The reaction mixture was stirred at 50 °C for 3 h under nitrogen atmosphere. Water was subsequently added and the mixture extracted with EtOAc. The organic layer was washed with water and dried over anhydrous Na₂SO₄ and evaporated (Table 2).

Synthesis of 1H-benzimidazole-2-acetamide derivatives 14a-f

A mixture of related ethyl 1H-benzimidazole-2-acetates 13a-d (1 mmol) and appropriate ethylene or propylenediamines

(2 mmol) was stirred and heated at 100 °C for 7 h. The reaction mixture was dissolved in EtOAc and extracted with water. The organic layer was dried and evaporated (Table 2).

2-Acetamido-5-fluoro-6-(morpholin-4-yl)-1-propyl-1H-benzimidazole 15

A solution of 13e (0.3 g, 0.86 mmol) and NH₄Cl (0.46 g, 8.6 mmol) in EtOH (10 ml) was saturated with NH₃ for 1 h. The resulting suspension was stirred at room temperature for 24 h, then concentrated NH₄OH (10 ml, 50%) was added, and the suspension was further stirred at 50 °C for 24 h. The solvents were evaporated under reduced pressure. The residue was taken up in EtOAc and washed with 10% aqueous NaCl solution. The organic layer was dried, evaporated, and chromatographed (10% MeOH/ EtOAc) affording 0.17g (62 %) of 15 after crystallization from EtOAc/*n*-hexane. Mp 185–187 °C. NMR (DMSO-d₆) δ 0.9 (t, 3H), 1.69–1.75 (m, 2H), 3.0 (4H), 3.73 (6H), 4.25 (t, 2H), 7.16 (d, 1H, *J*_m = 7.7 Hz), 7.32 (d, 1H,

Table 2. Formulas, purification procedures, physical and spectral data of compounds 10a–g, 11c, 12a–e, 13a–e, and 14a–f.

| Comp. | Formula | Purification procedure | Yield (%) | Mp °C | NMR (δ ppm) | Mass (70 eV) |
|--------|--|---|-----------|----------------------|---|---|
| 10a | | | | 131 ^a | | |
| 10b | C ₁₅ H ₂₀ FN ₃ O ₂ · 0.3 H ₂ O | CHCl ₃ : n-Hexane (1 : 2) (flash chrom.) then recrystallization (ethanol) | 59 | 80-82 | (CDCl ₃) 0.65(m,2H), 0.9(m,2H), 1.05 (d,3H), 1.15(m,1H), 1.8(m,4H), 2.6 (t,2H), 2.9(m,1H), 3.7(t,2H), 6.5(d,1H, J _m = 8 Hz), 7.8(d,1H, J _o =14 Hz), 8.3(br.s,1H). | 294(M ⁺ , 10), 293(M ⁺ , 2), 247(35), 148(9), 69(12), 55(100). |
| 10c | | | | 150-151 ^b | | |
| 10d | C ₁₂ H ₁₆ FN ₃ O ₂ · 0.3 H ₂ O | CHCl ₃ : n-Hexane (1 : 2) (flash chrom.) then recrystallization (ethanol) | 61 | 119-121 | (CDCl ₃) 1.0(d,3H), 1.35(m,1H), 1.6-1.8 (m,4H), 2.8(m,2H), 3.7(m,2H), 6.0(3H), 7.8(d,1H, J _o =14 Hz). | 253(M ⁺ , 18), 109(16), 69(13), 55(58), 41(100). |
| 10e | C ₁₆ H ₁₇ FN ₄ O ₂ · 2.5 H ₂ O | CHCl ₃ : n-Hexane (1 : 2) (flash chrom.) then recrystallization (ethanol) | 58 | 173-175 | (CDCl ₃) 3.3(4H), 3.4(4H), 6.2(3H), 6.9-7.3(5H), 7.9(d,1H, J _o =14Hz) | 316(M ⁺ , 23), 183(12), 132(47), 105(100), 91(28), 77(73), 51(25). |
| 10f | C ₁₂ H ₁₆ FN ₃ O ₂ · 0.5 H ₂ O | CHCl ₃ : n-Hexane (1 : 2) (flash chrom.) then recrystallization (ethanol) | 63 | 117-119 | (CDCl ₃) 0.9(d,3H), 1.1(m,1H), 1.9(4H), 2.4(t,1H), 2.8(t,1H), 3.5-3.7(m,2H), 6.0(3H), 7.7(d,1H, J _o = 14 Hz). | 253(M ⁺ , 58), 252(27), 109(33), 83(48), 69(31), 55(100). |
| 10g | C ₁₃ H ₁₈ FN ₃ O ₃ | Recrystallization (ethanol) | 32 | 185 | (CDCl ₃) 1.1(t,3H), 1.7-1.8(m,2H), 3.2 (q,2H), 3.3(t,4H), 3.9(t,4H), 6.0(d,1H, J _m =8Hz), 7.8 (d,1H, J _o =14Hz), 8.3(br.s,1H). | 283(M ⁺ , 68), 254(43.7), 236 (43), 196(46), 83(60), 43(100). |
| 11c | | | | 94-95 ^c | | |
| 12a | C ₁₄ H ₁₈ FN ₅ O ₂ · 0.25 C ₂ H ₅ OH | Recrystallization (ethanol) | 60 | >280 | (DMSO-d ₆ - CDCl ₃) 2.4(s,3H), 2.6(4H), 3.0(4H), 3.9(s,3H), 7.1(d,1H, J _m =7.8Hz), 7.2(d,1H, J _o = 12.5 Hz), 11(br.s, 1H). | 307(M ⁺ , 7), 236(10), 204(18), 191(3), 177(9), 150 (5), 97(6), 83(60), 71(100). |
| 12b | C ₁₅ H ₂₀ FN ₅ O ₂ · 0.25 C ₂ H ₅ OH | Recrystallization (ethanol) | 58 | >280 | (DMSO-d ₆) 1.3(t,3H), 2.3(s,3H), 2.5 (4H), 3.3(4H), 4.25(q,2H), 7.0 (d,1H, J _m =7.9Hz), 7.2(d,1H, J _o =12.5Hz), 11.3(br.s, 1H). | 322(M ⁺ , 18), 250(14), 204(8), 178(35), 150(15), 123(12), 97(10), 85(15), 71(100). |
| 12c | C ₁₅ H ₁₉ FN ₄ O ₂ · 0.25 C ₂ H ₅ OH | Recrystallization (ethanol) | 53 | >280 | (DMSO-d ₆ - CDCl ₃) 1.0(d,3H), 1.4-3.4 (9H), 3.9(s,3H), 6.9(d,1H, J _m =7.6 Hz), 7.1(d,1H, J _o = 12 Hz), 11.5(br.s, 1H). | 307 (M ⁺ , 23), 274(12), 204(16), 177(14), 150(8), 122 (7), 85(15), 83(24), 59(100). |
| 12d | C ₁₆ H ₂₁ FN ₄ O ₂ · 0.25 C ₂ H ₅ OH | Recrystallization (ethanol) | 44 | >280 | (DMSO-d ₆ - CDCl ₃) 0.9(d,3H), 1.5(3H), 1.8-3.4(9H), 4.4(q, 2H), 7.1(d, 1H, J _m =7.9 Hz), 7.3(d,1H, J _o =12.4 Hz), 11.4 (br.s 1H). | 321(M ⁺ , 100), 319(43), 273(31), 247(40), 203(11), 177(21), 150(9), 83(10). |
| 12e | C ₂₀ H ₂₂ FN ₅ O ₂ · 0.5 H ₂ O | Recrystallization (ethanol) | 42 | >280 | (DMSO-d ₆ - CDCl ₃) 1.3(t,3H), 2.5(4H), 3.1(4H), 4.25(q,2H), 6.7-7.3(7H), 11.3(br.s 1H). | 384(M ⁺ , 12), 204(3), 177(11), 132(14), 105(100), 91(22), 77(56), 63(13), 51(15), 45(54). |
| 13a | | | | 142-144 ^d | | |
| 13b** | C ₂₀ H ₂₆ FN ₃ O ₂ | CHCl ₃ : n-Hexane (1 : 2) (flash chrom.) | 58 | * | | 359(M ⁺ , 100), 286(21), 216(9), 187(11), 119(6), 69(9), 55(29), 41(58). |
| 13c** | C ₁₆ H ₂₁ FN ₄ O ₂ | CHCl ₃ : n-Hexane (1 : 2) (flash chrom.) | 53 | * | | 321(M ⁺ , 14), 249(5), 176(11), 149(3), 121(3), 85(5), 71(64), 56(12), 43(100). |
| 13d** | C ₁₇ H ₂₂ FN ₃ O ₂ | CHCl ₃ : isopropanol (10 : 2) (flash chrom.) | 44 | * | | 319(M ⁺ , 100), 246(37), 176(68), 148(52), 121(25), 69(47). |
| 13e | C ₁₈ H ₂₄ FN ₃ O ₃ | EtOAc : n-Hexane (1 : 1) (flash chrom.) | 32 | 116-118 | (CDCl ₃) 1.0(t,3H), 1.3(t,3H), 1.8-1.9(m, 2H), 3.1(t,4H), 3.9(t,4H), 4.0(s,2H), 4.1 (t,2H), 4.2(q,2H), 6.8(d,1H, J _m =8 Hz), 7.4 (d,1H, J _o = 12 Hz). | 349(M ⁺ , 100), 291(21), 276(27), 218(18), 105(24), 83(54), 43(97). |
| 14a | C ₂₀ H ₃₁ FN ₆ O · 3 HCl · 2.3 H ₂ O | CHCl ₃ : isopropanol (2 : 1) then recrystallization (ethanolic HCl) | 21 | * | (D ₂ O) 1.3-1.4(t,6H), 3.1(s,3H), 3.3-3.8 (18H), 7.5(d,1H, J _m =8 Hz), 7.6 (d,1H, J _o = 11.2 Hz). | 390(M ⁺ , 2), 159(5), 130(14), 122(57), 104(100), 86(67), 76(61). |
| 14b | C ₂₁ H ₃₁ FN ₆ O · 3 HCl · 2.8 H ₂ O | CHCl ₃ : isopropanol (2 : 1) then recrystallization (ethanolic HCl) | 21 | * | (D ₂ O) 1.2-1.3(2H), 1.4-1.5(2H), 3.0-3.8(24H), 7.6(d,1H, J _m =7Hz), 7.7(d,1H, J _o =11Hz). | 402(M ⁺ , 23), 344(8), 331(14), 314(20), 287(15), 216(8), 98(12), 70(100). |
| 14c | C ₂₂ H ₃₂ FN ₅ O · 2 HCl · 5H ₂ O | CHCl ₃ : isopropanol : NH ₃ (20 : 5 : 0.1) then recrystallization (ethanolic HCl) | 25 | * | (D ₂ O) 1.0(d,3H), 1.2(2H), 1.4(2H), 1.9-2.3 (5H), 2.9-3.9 (17H), 7.8 (d,1H, J _o =11 Hz), 8.0 (d,1H, J _m = 6.4 Hz). | 402 (M ⁺ , 3), 331(3), 314(4), 288(3), 189(2), 71(3), 58(100). |
| 14d*** | C ₂₄ H ₃₆ FN ₅ O · HCl | CHCl ₃ : isopropanol (2 : 1) then recrystallization (ethanolic HCl) | 24 | * | (D ₂ O) 1.1(d,3H), 1.2(2H), 1.3-1.4(8H), 2.0-2.2(5H), 3.3-4.0(15H), 7.8(d,1H, J _o =11.3 Hz), 8.0 (d,1H, J _m =6.5 Hz), 8.2 (s,1H). | 430(M ⁺ , 1), 331(2), 113(1.5), 99(4), 86(100), 58(17). |
| 14e | C ₂₃ H ₃₅ FN ₆ O · 2 HCl · 2 H ₂ O | CHCl ₃ : isopropanol (3 : 2) then recrystallization (ethanolic HCl) | 13 | * | (D ₂ O) 1.1(2H), 1.1-1.3(8H), 2.4-3.5(20H), 3.9(s,2H), 7.1(d,1H, J _m =7.7 Hz), 7.4(d,1H, J _o =12.5 Hz). | 430(M ⁺ , 3), 331(6), 314(3), 86(100), 70(11), 58(19). |
| 14f | C ₂₂ H ₃₃ FN ₆ O · 1.6 H ₂ O | CHCl ₃ : isopropanol : NH ₃ (2 : 1 : 0.1) | 65 | * | (DMSO-d ₆) 1.1(2H), 1.3(2H), 1.9(2H), 2.5-3.6(22H), 4.1(s,2H), 7.4(d,1H, J _m =7.4 Hz), 7.7(d,1H, J _o = 11.6Hz). | 416 (M ⁺ , 38), 314(30), 287(3), 83(7), 70(24), 58(100). |

a) Ref [13] : 130 °C , b) Ref [12] : 152-153 °C , c) Ref [11] : 96-97 °C , d) Ref [13] : 143-145 °C , * : Hygroscopic and with no sharp mp, ** : Since these intermediates are gummy solids no attempt was made to perform elemental and NMR analysis, ***: It is very hygroscopic and does not give satisfactory elemental analysis results.

$J_0 = 12.8$ Hz). MS: m/z 320 (M^+ , 10), 276 (4), 235 (4), 176 (4), 44 (100). Anal. ($C_{16}H_{21}FN_4O_2$) C, H, N.

1-Cyclopropyl-2-ethyl-5-fluoro-6-(4-methylpiperazin-1-yl)-1H-benzimidazole 16

A suspension of **13a** (0.3 g, 0.8 mmol) in DMF (0.5 ml) was hydrogenated over 10% Pd/C. After dilution with EtOAc and filtration, the solution was extracted with water and the organic layer dried and evaporated. The residue was purified by column chromatography ($CHCl_3$) and recrystallized from isopropanol, yielding 0.16 g (66%) of **16**, mp 172–174 °C. NMR ($DMSO-d_6$) δ 0.9 (2H), 1.2 (2H), 1.3–1.4 (t, 3H), 2.2 (s, 3H), 2.5 (4H), 2.9–3.0 (q, 2H), 3.3 (4H), 7.1 (d, 1H, $J_m = 7.8$ Hz), 7.3 (d, 1H, $J_0 = 12.8$ Hz). MS: m/z 302 (63.97), 287 (7.26), 232 (14.15), 217 (18.01), 203 (25.37), 189 (5.38), 175 (8.55), 148 (4.92), 121 (5.19), 108 (2.42), 101 (2.99), 98 (2.72), 71 (100). Anal. ($C_{17}H_{23}FN_4$) C, H, N.

References

- [1] M. S. Bartlett, T. D. Edlind, M. M. Durkin, M. M. Shaw, S. F. Queener, J. W. Smith, *Antimicrobial Agents Chemotherapy* **1992**, *36*, 779–782.
- [2] M. S. Bartlett, T. D. Edlind, C. H. Lee, R. Dean, S. F. Queener, M. M. Shaw, J. W. Smith, *Antimicrobial Agents Chemotherapy* **1994**, *38*, 1834–1837.
- [3] T. D. Edlind, Tu L. Hang, and P. R. Chakraborty, *J. Infectious Diseases* **1990**, *162*, 1408–1411.
- [4] M. C. Cruz, M. S. Bartlett, T. D. Edlind, *Antimicrobial Agents Chemotherapy* **1994**, *38*, 378–380.
- [5] S. K. Katiyar, V. R. Gordon, G. L. McLaughlin, T. D. Edlind, *Antimicrobial Agents Chemotherapy* **1994**, *38*, 2086–2090.
- [6] D. K. Schmidt, H. F. Jordaan, J. W. Schneider, J. Cilliers, *Int. J. Dermatol.* **1995**, *34*, 574–579.
- [7] D. H. Taylor, K. S. Richards, and D. L. Morris, *J. Helminthol.* **1989**, *63*, 349–352.
- [8] R. A. Coburn, M. T. Clark, R. T. Evans, R. J. Genco, *J. Med. Chem.* **1987**, *30*, 205–208.
- [9] E. A. M. Badawey, Y. M. Gohar, *Farmaco* **1992**, *47*, 489–496.
- [10] L. Garuti, G. Giovanninetti, A. Ferranti, A. Chiarini, G. Bertocchi, P. Sabatino, P. Brigidi, *Pharmazie* **1987**, *42*, 378–381.
- [11] M. M. El-Abadelah, S. S. Sabri, M. H. Abu Zarga, R. J. Abdel-Jalil, *Heterocycles* **1995**, *41*, 2713–2728.
- [12] M. M. El-Abadelah, M. Z. Nazer, N. S. El-Abadla, H. Meier, *Heterocycles* **1995**, *41*, 2203–2219.
- [13] C. Hubschwerlen, P. Pflieger, J.-L. Specklin, K. Gubernator, H. Gmünder, P. Angehrn, I. Kompis, *J. Med. Chem.* **1992**, *35*, 1385–1392.
- [14] H. L. Kloppe. U.S. **1960**, 2,933,504, April 19. *Chem. Abstr.* **1961**, *55*, 9431e.
- [15] H. L. Kloppe. U.S. **1960**, 2,933,502, April 19; *Chem. Abstr.* **1961**, *55*, 3617f.
- [16] R. Dubey, S. Abuzar, S. Sharma, R. K. Chatterjee, J. C. Katiyar, *J. Med. Chem.* **1985**, *28*, 1748–1750.
- [17] S. A. Glickman, A. C. Cope, *J. Am. Chem. Soc.* **1945**, *67*, 1017–1020.
- [18] S. Özbey, C. Kus, H. Göker, *Anal. Sci.* **2001**, *17*, 1019–1020.
- [19] H. Göker, M. Tunçbilek, G. Ayhan, N. Altanlar, *Farmaco* **1998**, *53*, 415–420.
- [20] F. Swarts, *Bull. Classe Sci. Acad. Roy. Belg.* **1913**, 241–278.
- [21] G. C. Finger, R. E. Oesterling, *J. Am. Chem. Soc.* **1956**, *78*, 2593–2596.